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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,735	GODDARD ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon, Ph.D	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-13 and 17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-13 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment and Declarations under 37 CFR § 1.132, both submitted 7 January 2005, have been entered. Claims 9, 10 and 14-16 are cancelled. Claims 1-8, 11, 12 and 14 have been amended. Claims 1-8, 11-13 and 17-20 are under examination in the Instant Application.

2. The Office acknowledges the previous submission of drawing on 5/8/2002.

3. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

4. The objection to the specification is withdrawn in response to Applicants changing the title.

5. The objection to the specification is withdrawn in response to Applicants providing a copy of the sequence listing in response to the "Notice to Comply".

6. Applicants request for correction of inventorship under 37 CFR 1.48(b) is acknowledged.

7. The Office acknowledges the submission of BLAST searches in the exhibit.

Claim Objections

8. Claim 19 is objected to because of the following informalities: It appears that Applicants have amended the claim. However, the claim identifier does not indicate that it is "currently amended". Appropriate correction is required.

Priority

9. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119. Applicants have argued that they are entitled to

the benefit of the filing date of August 24, 2000 based on the disclosure amplification data in PCT/US00/23328. Specifically, Applicants contends that based on the data in example 18, the differential expression in normal rectum versus rectal tumor tissue of the message confers to utility to PRO1774 encoding polynucleotides. Although, the previous patent application discloses the same polynucleotide and polypeptide sequences (SEQ ID NO: 127 and 128) as the instant specification and show differential expression, the disclosure is not enabling under 35 U.S.C. § 112 as required under 119(e). Therefore, the filing date of the instant application (8 May 2002) is considered as the priority date.

35 USC § 112, second paragraph, withdrawn

10. The rejection of Claims 1-8 and 17-20 under 35 U.S.C. 112, second paragraph, for being indefinite is withdrawn. Applicants' arguments and amendments to the current claims have necessitated the withdrawal of the rejections (7 January 2005).

35 U.S.C. § 112, first paragraph, Written Description withdrawn

11. The rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, Written Description, is *withdrawn* with respect to the recitation of "extracellular domain" and "signal peptide" because Applicants have amended the claims and described it. Thus, necessitating the withdrawal (7 January 2005).

35 U.S.C. § 112, first paragraph, Enablement withdrawn

12. The rejection of claim 1-6 under 35 U.S.C. § 112, first paragraph, scope of enablement, is *withdrawn* with respect to the recitation of "extracellular domain" and

"signal peptide" because Applicants have amended the claims and described it. Thus, necessitating the withdrawal (7 January 2005).

35 USC § 112, first paragraph – Enablement, maintained

13. The rejection of claims 1-5 and 17-20 under 35 U.S.C. 112, first paragraph, because the specification does not enable one of skilled in the art to which it pertains, or with which it is most closely connected, to make and/or use the invention commensurate in scope with these claims. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 5-9 of the previous Office Action (06 October 2004).

~~Although~~, the Office had previously indicated that the utility of the invention based on the sequence identity of SEQ ID NO: 128 to that of human alcohol dehydrogenase described by Meyers et al. (AAB84364, WO 01/44446, Pub. Date 06/01). The role of ADH activity in colorectal cancer was described on page: 4. However, Applicants assert that the claimed polynucleotides are useful as a diagnostic tool; based on the data that PRO1774 cDNA is more highly expressed in normal rectal tissue compared to rectal (see pages 11-17 of Applicants response of 7 January 2005).

In the instant case, the specification provides data showing that polynucleotide encoding PRO1774 is more highly expressed in normal rectal tissue compared to rectal tumor tissue. However, there is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in the normal tissue compared to the tumor tissue and as such the disclosure is not enabling. In addition, the specification does not teach what is the normal level of

expression, does not indicate how high or low the expression level is compared to for example, rectal tumor; and does not provide a statistical correlation to the level of expression (for example, there is no indication of how many samples were compared to study the expression).

As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that twenty-eight of the 165 protein spots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (abstract). In addition, it is stated that no significant correlation between mRNA and protein expression was found (r=-0.025) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient also varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a subset of the proteins exhibited a significant correlation with mRNA abundance.

The literature also cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between

breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Given the increase in expressed message for PRO1774 in the normal rectal tissue compared to rectal tumor tissue, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a higher cDNA expression would correlate with increased polypeptide levels. Further research needs to be done to determine whether the increase in PRO1774 cDNA expression in normal rectal tissue compared to rectal tumor tissue supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure.

The declarations of Mr. Grimaldi, filed under 37 CFR 1.132 (7 January 2005), is insufficient to overcome the rejection of claims 1-5 and 17-20, based upon 35 U.S.C. § 112, first paragraph as set forth in the last Office action. Similarly, the declaration of Dr. Polakis, filed under 37 CFR 1.132 (7 January 2005), is insufficient to overcome the rejection of claims 1-5 and 17-20, based upon 35 U.S.C. § 112, first paragraph as set forth in the previous Office action mailed on 06 October 2004. Likewise, the declaration of Dr. Ashkenazi, filed under 37 CFR 1.132 (7 January 2005), is insufficient to overcome the rejection of claims 1-5 and 17-20, based upon 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

In the declaration filed under37 CFR 1.132 (7 January 2005, originally filed in application serial number 10/063,557), senior research associate Mr. Grimaldi states (page 2, paragraph 5), that "data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual". In addition, Mr. Grimaldi declaration on paragraphs 6 and 7 states that semi-quantitative analysis employed to generate the data of example 18 is sufficient to determine if a gene is over or under expressed in tumor cells compared to corresponding normal tissue. Further it asserted that that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA expression between the tumor tissue and the counterpart normal tissue. Mr. Grimaldi also asserted that, if a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor. It is further stated that additional studies can then be conducted if further information is desired. In paragraph 7, declarant indicates that the difference in the gene expression is expected to be reflected in the difference in the corresponding protein. However, this appears to be declarant's opinion, and is not supported by fact or evidence. There is no description in the specification to that would indicate a correlation with higher or lower expression levels of the message to the PRO1774 polypeptide. It remains that; there is no information on the record as to whether the claimed protein is expressed at all in the rectal tissue, cancerous or otherwise. In addition, the specification does not teach what is the normal level of expression, does not indicate how high the expression level is compared to for example,

rectal tumor tissues; and does not provide a statistical correlation to the level of expression (for example, there is no indication of how many samples were compared to study the expression). Furthermore, it remains that, as evidenced by prior art described above the issue is simply not predictable, and the specification presents a mere invitation to experiment. Applicants citing the second Grimaldi declaration (exhibit 2) filed under 37 CFR § 1.132 argues that, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed..... this same principal applies to gene under-expression." Again citing paragraph 5, Applicants contend that 'the detection of increased mRNA expression is expected to result in increased polypeptide expression, and detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for the diagnosis and treatment." At paragraph 4 of the second Grimaldi declaration (Exhibit 2), the declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment. The PRO1774 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation

of PRO1774 is known to occur. All that the specification demonstrates is that the PRO1774 mRNA was more highly expressed in normal rectal tissue compared to rectal tumor tissue. No mutation or translocation of PRO1774 gene has been associated with for example, rectal tumor. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO1774 is present in higher levels in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 11 for the claimed polynucleotides because undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

The Polakis declaration states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that identify and could possibly be used to down regulate the PRO peptides. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr Polakis characterizes the instances where such a correlation does not exist as exceptions to the rule. Only Dr. Polakis conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Furthermore, unlike the teachings of Dr. Polakis, in the instant invention the message in normal tissue is over-expressed compared to the tumor tissue. Thus, the direct relevance of this reference is unclear. Applicants along with Mr. Grimaldi and Dr.

Polakis declarations also provide teachings from Molecular Biology of the Cell by Bruce Alberts to support their assertion that there is a correlation between increased gene expression and increased protein expression (page: 14). However, in contrast Chen et al. (2002) teach that there is no correlation between mRNA levels and proteins because of post-translational mechanisms account for the regulation of the abundance of protein (page: 313).

Applicants also refer to three additional articles (Orntoft et al., Hyman et al., and Pollack et al. as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Applicants characterize Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed corresponding increase in mRNA transcripts. Applicants further characterize Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. It is also claimed by the Applicants that Pollack et al. teach that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding mRNA expression of an individual gene, which may or may not be in a chromosomal region, which that is highly expressed. Orntoft et al. concentrated on

regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO1774 in the instant specification. That is, it is not clear whether or not PRO1774 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear. Hyman et al. also used CGH approach in their research. Less than half (44%) of highly amplified genes showed over expression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not provide additional supporting disclosure for the polynucleotide encoding the polypeptides of the instant invention to be sued in diagnostics. Pollack et al. using CGH technology, concentrate on large chromosome regions showing high amplification (p.12965). However, Pollack et al. did not investigate or show a relationship with amplification and polypeptide expression. In fact the authors caution that elevated expression of an amplified gene cannot alone be considered strong independent evidence of candidate oncogene's role in tumorigenesis (p.12968). Thus, these references collectively do not teach as Applicants contend that there is a direct correlation between increased mRNA levels and increased levels of encoded protein. Given the prior art teachings one of skilled in the art will not be able make and/or use the instant invention in cancer diagnostics.

Applicants also contend that the claimed polynucleotide encoding the polypeptide PRO1774 would have diagnostic value even if there is no positive correlation between gene expression and expression of the encoded polypeptide. Further, it is asserted that even if there was no correlation between gene expression and increased or decreased protein expression for PRO1774, the gene that is over-expressed or under expressed in

cancer would be useful in diagnosing cancer. Applicants assert that this position is supported by the declaration filed under 37 CFR 1.132 (7 January 2005) by staff scientist Ashkenazi. It claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (pages 1-2, declaration, 7 January 2005) and to identify cancers for which there was an absence of gene product over-expression (page 2). The Ashkenazi declaration further argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment.

Applicants provide evidence in the form of a publication by Hanna et al. (attached to the response of 7 January 2005). Applicants contend that the publication teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically.

In the instant application cDNA expression studies were conducted using pooled samples of normal and tumor tissues. With reference to Grimaldi reference, this appears to be declarant's own opinion, and is not supported by fact or evidence. The

specification describes only mRNA expression data. The specification does not teach what is the normal level of expression, does not indicate how high the expression level is compared to for example, normal esophageal tissues; and does not provide a statistical correlation to the level of expression (for example, there is no indication of how many samples were compared to study the expression). The argument presented evinces that instant specification provides a mere invitation to experiment, requiring undue experimentation of the skilled artisan to make and/or use the claimed invention in its full scope. The declaration does not provide data such that the examiner can independently draw conclusions. In addition, there is no evidentiary art that would corroborate for example, that "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue." Furthermore, as indicated above the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al discussions above). It is also not known whether PRO1774 polypeptide is expressed in for example, the normal rectal tissue and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO1774 is expressed more highly in normal rectal tissue compared to rectal tumor tissue and invites the artisan to determine the rest of the story. This is further borne out by Grimaldi assertion that "additional studies can then be conducted if further information is desired" (Appendix 1, paragraph 7). Such is insufficient to meet the requirements of 35 U.S.C. § 112, first paragraph for the claimed

nucleotide. Although, Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. It further contends that increased mRNA levels in tumor cells correlates with increased protein expression. However, in the instant invention the increased mRNA expression is observed in the normal tissues and not in the tumor tissues. In addition, there is no nexus to the polypeptide of PRO1774 disclosed in the specification. Therefore the declaration is insufficient to overcome the rejection of claims 1-5 and 17-20 based upon 35 U.S.C. § 112, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels.

Furthermore, the declarations do not provide data such that the examiner can independently draw conclusions. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes, that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). In addition, as

discussed above Chen et al. disclose that the correlation between mRNA expression and protein expression is poor at best in carcinomas.

The declaration of Ashkenazi appears to argue that even if there was no correlation between gene expression and increased or decreased protein expression for PRO1774, the polypeptide encoded by a gene that is over-expressed or under expressed in cancer would still have therapeutic value. The examiner agrees that evidence regarding lack of over-expression would also be useful. However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such.

Applicants claim regardless of the cause of the differential expression, the fact that there is a higher level of expression of PRO1774 gene in the normal rectal tissue compared to rectal tumor tissue, allows this gene expression to be used as a diagnostic tool. These arguments have been fully considered but are found not to be persuasive because there is no nexus between the differential expression of the cDNA in the instant invention and rectal tumors. In addition, the lack of information on the record whether the claimed protein (PRO1774) is expressed at all in rectal tissue, cancerous or otherwise would make significant further research a necessity.

At page 15, Applicants assert that the claimed nucleotides would have diagnostic utility even if there is no positive correlation between gene expression and expression of the encoded protein. The position of the Office is such that, one cannot extrapolate the expression data provided in the specification to support the implicit assertion that the polynucleotides encoding PRO1774 can be used in cancer diagnosis or therapy. These

arguments have been fully considered but are not found to be persuasive. Haynes et al., and Chen et al. teachings listed above and discussed contradict Applicants assertion that there exists a direct correlation between mRNA levels and the level of expression of the encoded protein. In fact, the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues (Hu et al.).

Although, Applicants indicate on p.15 that there is a well established correlation in the art that the level of protein is positively correlated to the level of mRNA, as indicated above Haynes et al. and Chen et al., polypeptide levels cannot be accurately predicted from mRNA levels. Therefore, there is no evidence to support Applicants' assertion that there is working hypothesis, among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels. In addition, the specification does not teach what is the normal level of expression in rectal tissue, does not indicate how high the expression level is compared to for example, rectal tumor tissues; and does not provide a statistical correlation to the level of expression (for example, there is no indication of how many samples were compared to study the expression). The declarations and cited references do not provide additional direction or guidance for the claimed nucleotides encoding the PRO1774 polypeptide. As stated above, the specification does not provide sufficient guidance to the skilled artisan to diagnose or treat any disease. Therefore, in the absence of any direct correlation between mRNA levels and protein levels PRO1774 or any supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is

also differentially expressed in the normal tissue compared to the tumor tissue, one of skill in the art would make and/or use the claimed invention in its full scope.

Furthermore, SEQ ID NO: 127 or fragments of such that are usable as hybridization probes and are not enabled for polynucleotides 80, 85, 90, 95 or 99% identical to such, nor which encode a protein 80, 85, 90, 95 or 99% identical to the protein of SEQ ID NO: 128, nor polynucleotides which hybridize to any of the above because there is no structural or functional information provided in the specification. In addition, the lack of direction/guidance presented in the specification regarding which variants of polynucleotides of SEQ ID NO: 127 encoded proteins would retain the desired activity, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the absence of working examples directed to variants and the breath of claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Although, Applicants have amended the claims to assert that the nucleic acid is more highly expressed in normal rectal tissue compared to rectal tumor tissue, or wherein the nucleic acid encodes a polypeptide that is more highly expressed in normal rectal tissue compared to rectal tumor tissue, there is no way of knowing which, if any variants would have the same property of higher expression in the specific tissue. There is no nexus between the degree of homology and regulation of gene expression. Until one identifies a particular variant that demonstrates a higher expression or not, one of skilled in the art would not know the expression profile of the variant. Modifications to

polynucleotides encoding the protein, e.g., by substitutions or deletions, would often result in deleterious effects to overall activity and effectiveness of the protein. Furthermore, it is also well known in the art that hybridization under moderately stringent conditions would yield nucleic acid molecules that are structurally unrelated.

Accordingly, the disclosure fails to enable such a myriad of the claimed nucleic acid molecules that not only vary substantially in length but also in nucleic acid composition and to provide any guidance to one skilled in the art on how to make and use the claimed genus of nucleic acid molecule. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed genus of the molecules embraced by the instant claims. Therefore, the rejections of record are maintained.

35 USC § 112, first paragraph – Written Description, maintained

15. Claims 1-5 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention is maintained. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 9-11 of the previous Office Action (06 October 2004). Briefly, the Applicants were not in possession of all or a significant number of polypeptides that have 80-99% homology to SEQ ID NO: 128 and still retain the function of SEQ ID NO: 128.

Applicants discuss the legal standards applied when evaluating Written Description, including the requirement that written description depends on the nature of

the invention and the amount of knowledge imparted to those skilled in the art by the disclosure (page 19, 7 January 2005). The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case. However, Applicants have not described or shown possession of all polypeptides 80-99% homologous to SEQ ID NO: 128, that still retain the function of SEQ ID NO: 128. Nor have Applicants described a representative number of species that have 80-99% homology to SEQ ID NO: 128, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 128.

As discussed in the previous Office Action (6 October 2004) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1774 polypeptides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein the isolated nucleic acid is more highly expressed in normal rectal tissue compared to rectal tumor tissue, or wherein the isolated nucleic acid encodes a polypeptide that is more highly expressed in normal rectal tissue compared rectal tumor tissue," (amended claims, 7 January 2005), is not adequate to describe polynucleotides encoding the PRO1774 polypeptides that have 80-99% homology to the PRO1774 polypeptide, since there was no reduction to practice to support the amended claims. Specifically, there is no way of knowing which, if any variants would have the same property of higher expression in the specific tissues. There is no nexus between the degree of homology and regulation of gene

expression. Until one identifies a particular variant that is highly expressed or not, one of skilled in the art would not know the expression profile of the variant. The mere sequence alone will not allow one of skilled in the art to predict expression. Applicants made no variant polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

Claim Rejections - 35 USC § 102, maintained

16. Claims 1-8, 13 and 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyers et al. (AAB84364, WO 01/44446, Pub. Date 06/01) is maintained. Applicants' arguments with respect to obtaining an earlier priority are not persuasive for reasons indicated above in paragraphs 9 and 13a. Thus, the filing date of 8 May 2002 is considered as the priority date. Therefore, the rejection of record is maintained.

Claim Rejections - 35 USC § 102(b), withdrawn

17. The rejection of claims 14-16 under 35 U.S.C. 102(b) as being anticipated by Birren et al. (AC003042/c, Pub. Date 07/98) is withdrawn because Applicants have cancelled these claims. Thus, obviating the rejection.

18. No claims are allowed.

19. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JANET ANDRES
PRIMARY EXAMINER